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CORRESPONDENCE

Restrictive dermopathy in a Taiwanese newborn

Dear Editor,

A male infant with a birth weight of 1030 g was born to a 37-year-old, G5P4 Taiwanese mother at 30 weeks and 1 day of gestation by cesarean delivery because of the preterm, premature rupture of the fetal membrane. The parents both belonged to the Taiwanese aboriginal tribe known as the Sediq, but they denied any consanguineous relationship. The infant was immediately sent to the neonatal intensive care unit because of respiratory distress.

Physical examination revealed a long transverse laceration on the neck and other small erosions on the flexor side of four extremities (Figures 1A and 1B). The infant was in a rigid position caused by generalized joint contractures. His skin was profusely shiny and taut with prominent subcutaneous vessels (Figure 1C). A characteristic face was observed with the following features: a fixed facial expression, hypertelorism, blepharophimosis, absence of eyelashes, eyebrows, a small pinched nose, microstomia, micrognathia, and malformed low-set ears (Figure 1D). A skin biopsy revealed hyperkeratotic epidermis, thinned dermis, and a flat dermoepidermal junction (Figure 2A). A histochemical stain showed abnormally dense collagen bundles aligned parallel to the epidermis and near absence of elastic fibers (Figure 2B). Subsequent genetic analysis of the zinc metalloprotease STE24 (ZMPSTE24) gene showed a homozygous nonsense mutation c.715G > T (p.Glu239X) in exon 6. In light of the clinical, pathological, and genetic findings, restrictive dermopathy (RD) was confirmed. Despite intensive care, however, the infant died 3 months later because of deteriorated pulmonary insufficiency.

RD is a rare and severe genodermatosis with an invariable lethal outcome. First recognized as a diagnostic entity in 1986 by Witt et al,[1] it is one of the laminopathies and is predominantly caused by lamin A–specific defects as a result of autosomal recessive (AR) mutations of the ZMPSTE24 gene.[2] Lamin A plays a fundamental role in preserving the integrity of the nucleus and in gene expression, DNA replication, and DNA repair.[3,4] It undergoes four post-translational processing steps from its precursor, prelamin A. The final modification is performed by ZMPSTE24, producing a nonfarnesylated mature lamin A.[2] Defects in the ZMPSTE24 gene lead to null or damaged activity of this enzyme, thereby accumulating excess immature prelamin A.

Diagnosis is based on clinical, histopathological findings and the result of genetic analysis. Characteristic dermatologic presentation includes facial dysmorphism (a fixed expressed face called Asian porcelain face, blepharophimosis, a small pinched nose, microstomia with an O-shaped mouth, micrognathia, and low-set ears); taut, shiny skin with prominent blood vessels; and contracture of all joints (arthrogryposis multiplex).[5] Pathological readings reveal hyperkeratotic epidermis, thin dermis, absence of rete ridges, collagen parallel to epidermis, and loss of elastic fibers.[6] With regard to genetic analysis, more than 20 mutations of ZMPSTE24 have been discovered.[2] The c.1085dupT in exon 9 is the most common mutation, found in 59.1% of patients.[2] Several hypotheses suggest possible pathogenesis, including alterations of epidermal proteins, defects of fibroblasts, abnormalities of elastic tissue, and impairment of collagen.[6] However, there is a lack of pathophysiological mechanisms to illustrate the relationships among genes, proteins, cells, and the clinical presentation of RD. The genotype and phenotype correlation remains to be fully elucidated.

In Taiwan, a total of 10 patients, including the present one, have been diagnosed with RD.[7] These patients possessed the same homozygous nonsense mutation c.715G > T and were born to parents who were heterozygous carriers of aboriginal tribe families (Atayal and Sediq); these tribes have an identical origin. Our patient lived for 3 months, which implies the residual function of the enzyme[3] or the advancement of medical care. According to previous literature, only ~60 cases have been reported worldwide as of 2009.[5] This disproportional racial ratio of cases between Taiwan and the rest of the world suggests a founder effect in the Austronesian aboriginal population because of migration and geographic isolation.[7] The risk of recurrence in subsequent pregnancies is 25% based on AR inheritance. Therefore, it is important to thoroughly provide genetic counseling and offer prenatal diagnostic tools to high-risk groups, such as mothers who have had children with RD or those with a positive family history, particularly in aboriginal tribes, to prevent this devastating disease. High-resolution ultrasonography may demonstrate representative features.[8] Moreover, pre-implantation genetic diagnosis and utilization of fetal DNA in maternal plasma may be beneficial for the early detection and reduction of complications from peripartum diagnostic examination.

In conclusion, RD has distinctive, consistent clinical and pathological features. Owing to its high incidence in Taiwanese aboriginal tribes, our dermatologists should be proficient in RD to make prompt and accurate diagnoses. Providing genetic counseling to families is essential to avoid the inevitable fatal outcomes in affected pregnancies.

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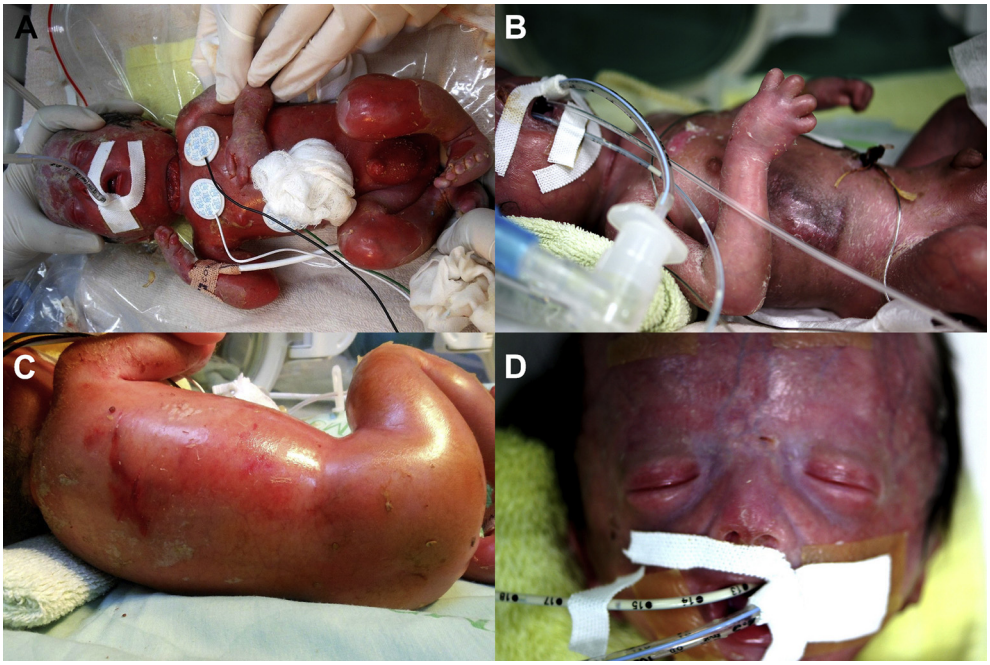

Figure 1 (A,B) Generalized joint contractures of the four extremities (arthrogryposis multiplex) and transverse laceration in the lower neck in response to the stress of delivery; (C) tense and translucent skin with prominent superficial vessels in the back, as well as several linear lacerations; (D) dysmorphic face: blepharophimosis, hypertelorism, antimongoloid slant, absence of eyelashes, eyebrows, small pinched nose, and microstomia with an O-shaped mouth.

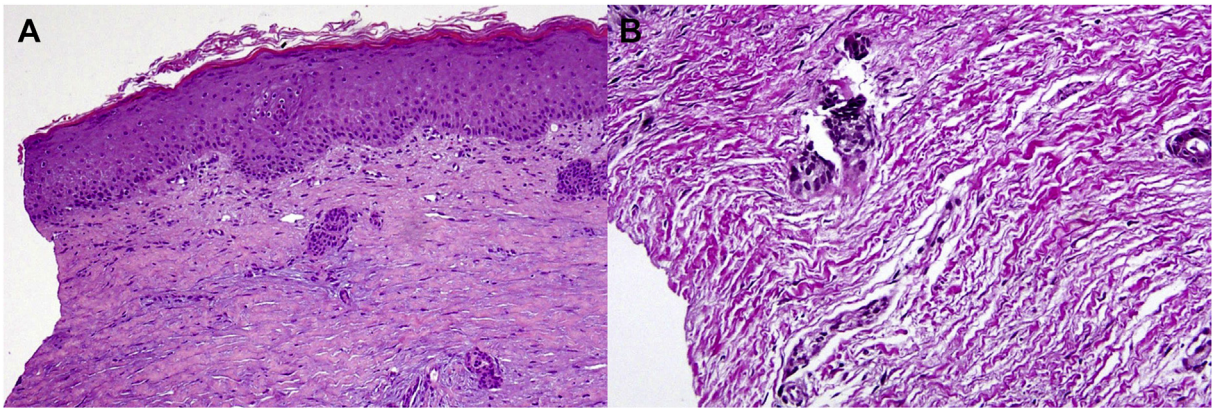

Figure 2 (A) A skin biopsy from the abdomen shows a thickened hyperkeratotic epidermis, thinned dermis, and flat dermoepidermal junction (hematoxylin–eosin, 100×); (B) Near absence of elastic fibers (Elastica Van Gieson stain, 200×).

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